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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

7590 04/27/2009

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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
04/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 8, 2009 has been entered.

2. Claims 1-41, 54-58, 70, and 74 have been canceled.

3. Claims 42-53, 59-69, 71-73, and 75-80 are under examination.

Rejections Maintained

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 42-53, 59-69, 71-73, and 75-80 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

Applicant's arguments filed February 10, 2009 have been carefully considered but they are deemed not to be persuasive. The response states in part that the

invention relates to the discovery that a class of molecules having a common structural motif (a CpG dinucleotide) provokes an immune response and when administered to a subject results in an immune response useful in the treatment of cancer. This class of oligonucleotides is described throughout the specification. Data is presented in vitro and in vivo using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The experiments demonstrated that the unmethylated CpG dinucleotide was the important component of the oligonucleotides by testing a number of control oligonucleotides in which the C was methylated or the C and/or G were replaced with other dinucleotides. The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. In view of the data in the specification the skilled artisan would have expected that virtually every CpG containing oligonucleotide would have the ability to provoke an immune response. Although some oligonucleotides may work better than others, it is expected that in general CpG oligonucleotides are immunostimulatory under the appropriate conditions.
At the time the priority patent application was filed it was known in the art that induction of interferon-3, (IFN-3,), IL-12, and IL-6, as well as NK cell activation was useful in the treatment of cancer (see response pages 7-8).

In response to this argument, as set forth in the previous office action, the specification discloses the immunostimulatory activity of oligonucleotides containing an unmethylated CpG dinucleotide, however, such disclosure does not enable a skilled artisan to treat cancer comprising administering oligonucleotides containing an

unmethylated CpG dinucleotide. The claims are drawn to a method of treatment of cancer comprising a huge genus of oligonucleotides containing an unmethylated CpG dinucleotide. The specification discloses that unmethylated CpG are effective at stimulating B-cell proliferation and cytokine secretion. The specification does not provide any working examples for treating any type of cancer by administering CpG oligonucleotides. The state of the art is such that there is a high degree of unpredictability in the treatment of cancer comprising administering any of a large genus of oligonucleotides containing an unmethylated CpG dinucleotide. In view of the unpredictability in the art, with regard to the treatment of cancers, one of ordinary skill in the art would require an undue amount of experimentation to practice the claimed method with all the oligonucleotides encompassed within the claims. Tonkunaga, et al. (Jpn. J. Infect. Disease, 1999, of record) teach administration of bacterial DNA was effective in some cases but efficacy was not significant and adverse reactions were rather severe (page 2). Trinchieri, et al. (Blood, 1994. of record) do not administer CpG dinucleotides, they administer cancer cells to induce an IL-12 response. Likewise, Brunda, et al. (Journal of Leukocyte Biology, 1994, of record) administer IL-12 to treat cancer, US PAT 4,883,662 (of record) administers a Parvovirus and Hayashi, et al. (Proceeding of the Japan Academy, 1994, of record) administer BCG-CWS to induce IFG-γ. None of these references speak to the use of CpG oligonucleotides to treat cancer.

Applicant further argues the class of CpG molecules as effective for treating cancer by providing co-pending applications that teach the induction of an immune

response (US PG PUB 2005/0059619, 2006/0211644, 2006/0140875, and 2008/0045473). While each of these references provide support for the CpG molecules being able to induce an immune response, there is no additional support provided for the treatment of cancer which is considered an unpredictable art. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Further, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Forni et al (Cancer Research, 2000, 60; 2571-2575) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with

established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy *in vivo*. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
April 16, 2009

/Anne M Gussow/
Examiner, Art Unit 1643